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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/760,121	01/16/2004	Steven P. Gygi	58056 (70207)	7370

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EXAMINER	
HAQ, SHAFIQUL	
ART UNIT	PAPER NUMBER
1641	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/760,121	GYGI ET AL.	
	Examiner	Art Unit	
	Shafiqul Haq	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *16-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Election/Restrictions

1. Applicants' response filed November 27, 2006 to election requirement in Office Action mailed December 28, 2005 (restart date 11/3/06) is acknowledged and entered.

2. Applicants' election with traverse of Group I, Claims 1-15 is acknowledged. Applicants must realize the search burden imposed on the examiner to search all the inventive groups in one application. The search for each of the distinct inventions of is not co-extensive particularly with regard to the literature search. Further, a reference that would anticipate the invention of one group would not necessarily anticipate or even make obvious another group. Finally, the condition for patentability is different in each case. A patentability determination for Invention of group I would require an assessment of the novelty and unobviousness of the tag molecule of claim 1 while a patentability determination for invention group II would require an assessment of the novelty and unobviousness of the combination of the tag moiety with other tag moieties having different isotopes and the patentability determination for invention IV would require an assessment of the novelty and unobviousness of the method steps. Thus, it will be an undue burden to examine all the inventive Groups in one application.

   Applicants have requested confirmation that if claim 1 is found to be allowable or if all of the claims are amended to include all the limitations of the allowable claim 1,

then all claims will be rejoined. With this regard, the examiner confirms that in the event that claim 1 is allowable, all claims dependent on claim 1 or the claims amended to include all limitations of claim 1, would be rejoined and examined together for patentability determination. However, Applicants must also realize that for rejoined claims 112 indefiniteness and enablement issues (specially with regard to some of the method claims) may arise which Applicants need to be addressed. Note that rejoinder of allowable product claims with process claims is addressed in paragraph 7 of 12/28/05 office action.

3. Claims 16-45 are withdrawn from further consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03 and claims 1-15 are examined on merits.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
6. Claim 1 recites the term "A reagent" in line 1 wherein the reagent comprises only of "a tag molecule". It is unclear what other components are present in the "reagent" for mass spectrometric analysis of proteins.
7. Claim 1, 3 and 6 recite "an isotope label" and "isotope". It is unclear what isotopes are intended to include by the term "an isotope label". Is the term "isotope label" also

includes normal isotopes (e.g. C^{12}). The term "isotope label" does not differentiate normally found isotopes (e.g. C^{12}) from higher proportion of isotopes (e.g. C^{13}). As for example, two samples can be labeled with two isotopes i.e. one having normal isotope (e.g. C^{12}) and one having higher isotope (e.g. C^{13}) for mass spectrometric analysis. Therefore, the term "isotope" label is not clear as to what isotopes are intended to include in this claim.

8. With respect to claim 1, the arrangement of different components (i.e. reactive sites, isotope label and anchoring site) in the tag molecule is unclear. The reactive site can be directly linked to anchoring site and either of the reactive sites or the anchoring site can be isotope labeled. Therefore, it is unclear how the reactive site, isotope label and anchoring site is arranged with respect to each other. Furthermore, the chemical nature and structure of the reactive site as well as the anchoring site is unclear. It is unclear whether the "site" comprises any reactive moiety or group that enables the "reactive site" and the "anchoring site" to form a stable association with a protein and to bind to solid support covalently.
9. Claim 2 recites the phrase "wherein the anchoring site of the tag molecule forms covalent bonds to a cis hydroxyl pair". It is unclear "cis hydroxyl pair" of what molecule or compounds are encompassed in this claim. Also it is unclear whether the "cis hydroxyl **pair**" is of the anchoring site of the tag molecule or of compounds attached to solid support to where the tag is bound.
10. With respect to claim 3, the general formula R-B(OH_2) is not correct. It is not clear whether applicants intended to mean R-B$(OH)_2$? The claim recites, "R group is a

suitable chemical moiety for incorporating the isotope". It is unclear what portion (i.e reactive moiety) of the compound R-$B(OH)_2$ functions as reactive site (for stably associating with a protein) and what portion of the compound functions as a pH sensitive anchoring site (for covalently anchoring the tag molecule to a solid support)? It is also noted that the recitation "for incorporating the isotope" is not a positive recitation and thus the it does not indicate the R group is incorporated with an isotope and which do not read on claim 1 as in claim 1, the tag molecule comprises and isotope label.

11. With respect to claim 4, it is not clear whether R represents the reactive site as recited in claim 1? It is so, then how the alkyl, aryl or cyclic group without any functional group can react to form stable bond with a protein.

12. With respect to claim 5, the position (location) of the isotope label in the compounds of phenyl-$B(OH)_2$ or hexyl-$B(OEthyl)_2$ is not clear. Claim 5 is dependent on claim 1 and the tag molecule recited in claim 1 comprises an isotope label.

13. With respect to claims 5, it is unclear whether the phenyl or the hexyl group in the tag molecule represent the reactive site as recited in claim 1? If it is so, then how the phenyl of hexyl group without any functional group can react to form stable bond with a protein.

14. Claim 14 recites the phrase "wherein the reactive site forms stable associations with a modified residue of a protein". It is unclear what "modified residues" is intended to encompass by the term "modified residue of a protein". The nature and structure of the "modified residue" is unclear.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1, 6-9, 11 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Aebersold et al. (WO 00/11208).

Aebersold et al. disclose a reagent for mass spectrometric analysis of proteins comprising a tag molecule having the formula A-L-PRG, wherein A represents a affinity tag, L is a linker and PRG is a protein reactive group (see abstract and page 5, lines 19-32). Aebersold et al. disclose that the linker group may be differentially isotopically labeled e.g. by substitution of one or more atoms in the linker with a stable isotope (see abstract and page 5, lines 19-32) (compare this with the recitation of "an isotope label" of instant application). Aebersold et al. disclose that the PRG group reacts selectively with a protein functional group to form a covalent or noncovalent bond stably tagging the protein as specific sites (see page 6, lines 7-15). Aebersold et al. further disclose that A functions as a molecular handle that selectively binds covalently to capture reagent (see page 5, lines 27-32). Specific example is cited in which biotin containing affinity tag (in which A is biotin) is used to tag proteins in a sample at their derivatized cysteine residues with PRG of the affinity tag and proteins bound to the affinity tag is then isolated by subsequent binding with an avidin coated agarose beads and biotinylated peptides are eluted

from avidin-agarose at a pH of 2 (see scheme 1 of page 74 and page 18, lines 25-30) (compare this with the recitation "pH sensitive anchoring site" in claim 1 of instant application). Therefore, all three components of the tag molecules of instant application (i.e. reactive site for associating with a protein, an isotope label and a pH sensitive anchoring site) are present in the affinity tag of Aebersold et al. and thus claim 1 of instant application is anticipated by Aebersold et al.

As for dependent claim 6, incorporation of stable isotopes such as stable isotope of oxygen, carbon, nitrogen, oxygen and sulfur are disclosed (page 11, lines 13-14). As for dependent claim 7, as described above, PRG of the affinity tag can form stable association with a protein and as for claim 8, Aebersold disclose labeling of peptited (see abstract). As for claim 11, as described above, affinity tag molecule attached to agarose beads are disclosed. As for claims 9 and 14, Aebersold et al. disclose that the PRG group binds to modified residues (e.g. disulfide bond of protein reduced to free SH i.e. sulfhydryl group) of a protein (see page 17, lines 14-15).

Therefore, the reference is deemed to anticipate the cited claims.

17. Claims 1-5, 10 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Sundrehagen et al. (US 5,631,364).

Claim 1 recites a tag molecule comprising a reactive site capable of associating with a protein, an isotope label and a pH sensitive reactive site capable of covalently anchoring the tag molecule to a solid support.

The recitation "for mass spectrometric analysis of protein" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. Applicant is reminded that a recitation of the intended use of the claimed invention, i.e. "for mass spectrometric analysis of protein", must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See In re Casey, 152 USPQ 235 (CCPA 1967) and In re Otto, 136 USPQ 458, 459 (CCPA 1963).

The recitation "for stably associating with a protein" and "for covalently anchoring the tag molecule to a solid support" are considered intended function of the groups and as long as functional group of a tag in a reference are capable of providing the intended function, then it meets the limitation.

Sundrehagen et al. disclose a labeled boronic acid derivative comprising a reactive site, a pH sensitive anchoring site {-B-$OH)_2$ } and a label (see abstract and compounds 4 and 5-11 of column 5). The reactive site (N-hydroxy-succinimide or amino group: see compounds 4 and 5-11) reads on the reactive site as it is capable of stably associating with a protein and the boronic acid portion {-$B(OH)_2$} reads on

the pH sensitive anchoring site as it is capable of covalently associating with a solid support having cis-diol (column 1, lines 30-43) and is pH sensitive. With respect to "label", Sundrenhagen et al. disclose that the label may be a chromophore, a fluorophore or a radionuclide" (colmn 1, lines 18-26).

The compounds 4 and 5-11 read on the tag molecule of claim 3 and 5 of instant application. Compare R group (aryl group, arylalkyl group) of claims 3 of present application with the phenyl group of compounds 4 and 5-11 of the reference. Also, compare the compound phenyl-B-(OH)2 of claim 5 of present application with the compounds 4 and 5-11 of the reference having phenyl group linked to a boronic acid group {-$B(OH)_2$}. With regard to the recitation "wherein the R group is a suitable chemical moiety for incorporating the isotope" in claim 3, it is the examiner's position that this is intended use language and the R group of the tag molecule do not have isotope incorporated in it. As to claim 10, Sundrenhagen et al. disclose NHS-CPBA (see column 10), 4-carboxy-phenylboronic acid (column 9) and compounds of 5-11 (column 5) and at least on of them is able to form aminal, carbonate or imine bond with a protein.

. As for claim 12, the compounds have a molecular weight that encompasses "about 175-300 daltons". Regarding the claim language "for forming surface of a biosensor utilizing surface plasmon resonance (SPR)" in claim 1 and the language in claim 2, it is the examiner's position that this is intended use language.

Therefore, the reference is deemed to anticipate the cited claims.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sundrehagen et al. (US 5,631,364) in view of Aebersold et al. (WO 00/11208).

See above teaching for Sundrehagen et al. regarding labeled boronic acid derivatives.

Sudrehagen et al. disclose labeling the boronic acid derivative with a chromophore of fluorophore (column 3, lines 60-67) and also disclose in the background use of radioisotope with boronic acid conjugate (column 1, lines 23-25 and 44-51) but however, differ from the instant application in failing to disclose labeling R group with isotope.

As discussed above, Aebersold et al. disclose a tag molecule having a reactive site, a pH sensitive anchoring site and an isotope label and further disclose that the linker group may be differentially isotopically labeled e.g. by substitution of one or more atoms in the linker with a stable isotope (see abstract; page 5, lines 19-32 and page 11, lines 9-14). Isotope labeling is advantageous because of its rapid and sensitive detection and Aebersold et al. disclose that by using tags having different isotopes incorporated therein, two or more samples can easily be compared by differentially labeling with the tags having different isotopes (i.e. light and heavy

isotopes) and differential labeling facilitates quantitative determination by mass spectrometry of relative amount of proteins in different samples (page 11, 9-14; page 7, lines 15-17 and page 5, lines 13-17).

Therefore, giving the above fact incorporation of isotopes in the linker of tag molecules provides rapid and sensitive detection of protein samples and facilitates quantitative determination of large number of samples by differential labeling (Aebersold et al.), it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate isotopes in the linker of the boronic acid conjugate for rapid and quantitative detection of different samples with a reasonable expectation of success.

20. Claims 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sundrehagen et al. (US 5,631,364) in view of Wagner (US 4,861,728).

See above teaching for Sundrehagen et al. regarding labeled boronic acid derivatives. Sudrehagen et al. envisioned using the labeled derivatives in an assay for cis-diols such as glycated blood proteins.

Sundrehagen et al. differ from the instant application in failing to disclose stable association of the reactive site with a modified residue of a protein.

Wagner in a detection method, discloses a labeled phenyl boronic acid conjugate that specifically binds with a modified residue of a protein. Wagner discloses that Boronic acid group binds to glycosyl residue of HbA1c (BbA1c is a glycosylated form of HbA) coated on a solid surface in order to detect glycosylated form of HbA to measure the percentage of glycosylated hemoglobin in blood (line 14 of column 3

through line 32 of column 3 and Fig. 5). Wagner also discloses that the method involving specific interaction of the label conjugate with glycosylated HbA is advantageous because it does not require separation step (line 66, column 1 to line 7, column 2) and thus this provides quick and efficient detection.

Therefore, use of the boronic acid compound of Sundrehagen et al. to bind modified residues of a modified protein (e.g. glycosylated proteins) to efficiently detect modified protein (Wagner) would be obvious to one of ordinary skill in the art as detection of modified residues of a protein with labeled boronic acid compound is taught in the method of Wagner.

Conclusion

21. The prior art made of record and not relied upon is considered pertiinent to applicant's disclosure.

Harbury et al., US Patent Application Publication Number 2003/0224448 A1, disclose that phenyl-$B(OH)_2$ or hexyl-$B(OEthyl)_2$ may be immobilized on a support (as in a boronate resin) (paragraph [0161]).

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shafiqul Haq whose telephone number is 571-272-6103. The examiner can normally be reached on 7:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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